

REMARKS

A. TELEPHONIC INTERVIEW CONDUCTED NOVEMBER 1, 2011

Applicants thank Examiner Wen and Supervisory Examiner Shukla for taking the time to discuss the pending claims in a telephonic interview conducted November 1, 2011. Agreement was not reached. Details of the Interview are discussed below.

B. AMENDMENTS TO THE CLAIMS

Claims 1-19, 26-36, and 45-61 are pending. Claims 26-36 and 45-61 are withdrawn from consideration, claim 13 is allowed, and claims 1-12 and 14-19 are currently under examination.

Claim 2 has been amended to recite that the amino acid sequence is the amino acid sequence of SEQ ID NO: 5. Claim 3 has been canceled. Claim 12 has been amended to conform to the disclosure in Example 1. No new matter has been added by way of the amendments.

C. THE OFFICE ACTION

The Office withdrew the rejection of claims 1-4, 6-10, 12, 14-16, and 19 under 35 U.S.C. § 102(e) for assertedly being anticipated by U.S. Patent No. 6,822,138 ("Schreiber"). The rejection of claims 1-10, 12, and 14-19 under 35 U.S.C. § 103(a) for assertedly being obvious over Schreiber in view of Green, *J Immun Methods*, 231, 11-23 (1999) (hereinafter "Green") and Owens et al., *J Immun Methods*, 168, 149-165 (1994) (hereinafter "Owens") was also withdrawn. The Office, however, rejected claims 1-10, 12, and 14-19 under 35 U.S.C. § 103(a) for assertedly being obvious over Greene et al. (U.S. Patent No. 6,265,538; hereinafter "Greene") in view of Ferran et al. (U.S. Publication No. 2001/0053769; hereinafter "Ferran"), Campbell (*Monoclonal Antibody Technology*, Chapter 1, pages 1-32 (1984); hereinafter "Campbell"), Green and Owens. Claim 11 was subject to objection for depending from a rejected claim but was otherwise allowable.

D. THE REJECTION UNDER 35 U.S.C. § 103(a) SHOULD BE WITHDRAWN.

The Office rejected claims 1-10, 12, and 14-19 under Section 103(a) for assertedly being obvious over Greene in view of Ferran, Campbell, Green and Owens. The rejection is respectfully traversed.

To establish a *prima facie* case of obviousness, the Office must establish that the art disclosed or suggested each claim-recited element, that there is a reason to modify a teaching or to combine teachings of multiple references, and that one of skill would have had a reasonable expectation of success in practicing the claimed subject matter. *See KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1731 (2007); *see also* M.P.E.P. §§ 2143.01-2143.03.

During the telephonic interview and several times in the Office Action, the Office asserted that Greene discloses the same peptide used in the instant application to successfully generate the claimed antibodies. *See, e.g.*, Office Action, page 3. Specifically, the Examiner asserted that Greene discloses that the activation loop of NIK corresponds to amino acids 534-566, (column 3, lines 59-62) and that amino acids 534-566 correspond to SEQ ID NO: 6. Applicants do not dispute that amino acids 534-566 correspond to the activation loop of NIK. The Office, however, is incorrect in asserting that amino acids 534-566 correspond to SEQ ID NO: 6. In fact, amino acids 534-566 correspond to SEQ ID NO: 4. Moreover, Example 1 of the application-as-filed demonstrates that only peptides with phosphorylated T559 at the penultimate position, *e.g.*, SEQ ID NO: 3, are able to successfully generate antibodies that specifically bind to NIK phosphorylated at T559. Focusing solely on amino acid position, it is apparent that an active site fragment of amino acids 534-566 does not, and cannot, place the phosphorylatable Thr (*i.e.*, T559) at a location next to a terminal amino acid. Position 559 is neither position 535 nor position 565, the two penultimate positions in Greene's peptide (*i.e.*, a peptide having amino acids 534-566, such as a SEQ ID NO: 4 peptide). In other words, a SEQ ID NO: 4 peptide does not generate antibodies that specifically bind NIK phosphorylated at T559. Further, Greene discloses neither SEQ ID NO: 3 nor SEQ ID NO: 6. Thus, Greene's disclosure of the peptide of SEQ ID NO: 4 neither discloses nor suggests a peptide capable of eliciting a claim-recited antibody. In fact, Greene would not be enabling for the production of antibodies that specifically bind NIK phosphorylated at T559 because the SEQ ID NO: 4 peptide of Greene would not generate the

desired antibodies, as described in Example 1. Certainly, generation of an antibody specific to NIK phosphorylated at T559 would not be predictable in view of the data in Example 1. Applicants are concerned that the outstanding Office Action does not recognize these facts or the necessary conclusions flowing therefrom, given that Applicants noted these facts and conclusions during the above-noted telephonic interview.

In the Office Action, the Office asserted that Greene discloses that phosphorylation of NIK at T559 is important in the activation of NIK. The Office acknowledged that Greene does not disclose antibodies raised against the activation loop comprising phosphorylated T559. The Office, however, asserted that it would have been obvious to a person of ordinary skill in the art to generate such antibodies because “1) making antibodies to a known antigenic target is a well-practiced technique in the art at the time of the invention was made as exemplified by Campbell (see entire document); and 2) there is a well-known need in the art to make and use specific antibodies that recognize the phosphorylated forms of NIK as exemplified by Ferran et al. (see entire document).” Office Action, p. 3. During the telephonic interview and several times in the Office Action, the Office erroneously asserted that Greene discloses the same peptide used in the instant application to successfully generate the claimed antibodies. Specifically, the Examiner asserted that Greene discloses the activation loop of NIK, corresponding to amino acids 534-566, and cited to column 3, lines 59-62. The Office then further erroneously asserted that amino acids 534-566 correspond to SEQ ID NO: 6. Green and Owens were relied on for teachings relating to human and chimeric antibodies, respectively, which are limitations present in the dependent claims.

The logic employed by the Office in regard to the new Section 103(a) rejection is identical to the logic employed in the Office Action mailed August 31, 2010. In that Office Action, the Office relied on Lin et al. (*Mol. Cell Biol.*, 18(10), 5899-5907 (1998); hereinafter “Lin”) as teaching the importance of T559 phosphorylation in the activation of NIK. The first named author, Lin, is also listed as an inventor on the Greene patent. Moreover, the subject matters disclosed in Greene and Lin are apparently identical. In the response to the August 31, 2010 Office Action filed February 17, 2011, Applicants argued that it was unpredictable to generate phospho-NIK-specific antibodies in view of Lin and other references cited in the August 31, 2010 Office Action. As evidence of the lack of

predictability, Applicants pointed to Example 1, which demonstrated polyclonal antibodies generated using three immunogenic fragments of the NIK activation loop comprising amino acids 553-566, amino acids 553-562, or amino acids 549-560. All of the immunogenic fragments comprised phosphorylated T559. Only the fragment comprising amino acids 549-560 (*i.e.*, SEQ ID NO: 3, where the phosphorylated threonine residue was in the penultimate position) produced antibodies specific to phosphorylated NIK. In the Office Action mailed May 2, 2011, the rejection was withdrawn in view of Applicant remarks that “only fragments containing 549-560 (*i.e.*, SEQ ID NO: 3) produced antibodies specific to phosphorylated NIK and that Lin did not teach or suggest the specific fragment set for in SEQ ID NO: 3.” See May 2, 2011 Office Action, page 4. None of Greene, Ferran, Campbell, Green or Owens discloses or suggests SEQ ID NO: 3, SEQ ID NO: 6, or any other NIK peptide placing the T559 residue in a penultimate position. It stands to reason that none of these references discloses or suggests a peptide useful in generating phospho-NIK-specific antibodies when used as an antigen. Accordingly, it is unclear why the Office has imposed a new rejection based on the same reasoning that was just persuasively rebutted, according to the Office. The Office has merely located a different reference (*i.e.*, the Greene patent) by essentially the same authors as the prior-cited Lin reference, which makes effectively the same substantive disclosure as Lin, to craft an obviousness rejection based on the same logic employed in the August 31, 2010 Office Action that was overcome in the May 2, 2011 Office Action.

Ferran is cited for the assertion that there was a well-known need to in the art for antibodies that recognize the phosphorylated form of NIK. It is important to note that Ferran did not actually make or use antibodies that specifically recognize phosphorylated NIK. Ferran certainly didn't disclose or suggest an antigenic peptide placing phosphorylated T559 in a penultimate, or any other, position to generate any phospho-specific antibody. Campbell was cited for the proposition that it is customary to make monoclonal antibodies against a macromolecule even without a clear objective for their application. Campbell wasn't cited as suggesting even the desirability of generating antibodies specific to post-translationally modified forms of a peptide, such as a phosphorylated T559 form of NIK. Unsurprisingly, Campbell doesn't disclose or suggest an antibody specific to NIK phosphorylated at T559 or a method that would predictably yield such an antibody, as by using a peptide with phosphorylated threonine in the penultimate position. Green and Owens

were cited as purportedly describing human, humanized, and chimeric antibodies or providing motivation for generating monoclonal antibodies. These references fail to cure the deficiencies of Greene in disclosing or suggesting each element of any of the rejected claims or in enabling the production of antibodies that specifically bind NIK phosphorylated at T559. Moreover, the instant application teaches use of a phospho-peptide (SEQ ID NO: 3 phosphorylated at T11, corresponding to T559 of SEQ ID NO: 5) to elicit antibodies specifically binding to phosphorylated NIK and not to non-phosphorylated NIK. *See* Example 1. None of Ferran, Campbell, Green or Owens discloses or suggests using a phospho-peptide of any kind to elicit antibodies and none disclosed or suggested the claimed antibodies specifically binding to phosphorylated NIK and not to non-phosphorylated NIK. Thus, the Office has not established a *prima facie* basis for rejecting the claims under § 103(a) because the Office has not established that the prior art discloses or suggests all the elements of the claims. Accordingly, the rejection of claims 1-10, 12, and 14-19 under 35 U.S.C. § 103(a) over Greene in view of Ferran, Campbell, Green and Owens, considered alone or in combination, has been obviated and should be withdrawn.

Additionally, the Office has not established that there would have been a reasonable expectation of success in combining the cited references to arrive at the claimed invention. The combination of Greene, Ferran, Campbell, Green and Owens does not disclose or suggest each element of any rejected claim in failing to disclose or suggest an antibody or fragment thereof that specifically binds to phosphorylated NIK but does not bind to non-phosphorylated NIK. Evidence in the instant application shows that the peptide disclosed in Greene and cited by the Examiner (*i.e.*, SEQ ID NO: 4, but erroneously identified by the Examiner as SEQ ID NO: 6) would not generate antibodies that specifically bind NIK phosphorylated at T559. Thus, had a person of skill in the art followed the teachings of Greene, Ferran, Green and Owens, as laid out by the Office, antibodies that specifically bind NIK phosphorylated at T559 could not have been predictably generated and, in fact, would not have been generated. The Office adopted the position that, “[g]iven that Greene et al. taught the activation loop, aa 534-566, which is Applicant’s SEQ ID NO: 6, it would have been obvious to make an antibody targeting that fragment of NIK.” Office Action, pp. 3-4. As noted above, Greene does not disclose SEQ ID NO: 6, but does disclose SEQ ID NO: 4. Because the fragment consisting of SEQ ID NO: 4 (*i.e.*, the actual fragment

disclosed in Greene) doesn't work in generating a phospho-specific antibody, Greene points away from, not towards, the claimed subject matter. In moving beyond Greene's active-site fragment, the Office relied on Ferran's disclosure of a desire to have phospho-NIK-specific antibodies. In addition to failing to make any such antibody, Ferran did not disclose or suggest use of a NIK peptide with T559 in the penultimate position for use as an antigen. Thus, the cited references in combination do not lead predictably to the phospho-NIK-specific antibody recited in the claims. Accordingly, the rejection of claims 1-10, 12, and 14-19 under 35 U.S.C. § 103(a) over Greene in view of Ferran, Campbell, Green and Owens, considered alone or in combination, has been overcome-in-part and rendered moot-in-part and the rejection should be withdrawn.

E. CONCLUSION

Applicants submit that the pending application is in condition for allowance. The Examiner is invited to contact the undersigned attorney by telephone if there are issues or questions concerning this submission that might be efficiently resolved in that manner.

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Respectfully submitted,

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